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Integrated Bioinformatics Analysis Reveals the Clinical and Epigenetic Significance of PYCR1 as a Diagnostic, Prognostic, and Therapeutic Biomarker in Lung Adenocarcinoma

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ABSTRACT

Lung adenocarcinoma (LUAD) is still one of the main causes of death from cancers globally; hence, there is a need for developing new biomarkers and targets for diagnosis and treatment. This work involves analyzing the involvement of Pyrroline-5-carboxylate reductase 1 (PYCR1) through multidimensional bioinformatic approaches on LUAD data obtained from 'The Cancer Genome Atlas (TCGA)' portal-UALCAN. Our findings indicate that PYCR1 is highly expressed in LUAD tissue samples than normal lungs ($p < 1E-12$) with a consistent increase in its expression irrespective of age group, gender, or smokers/non-smokers. Elevated PYCR1 was positively associated with more advanced clinical stages of tumors and lymph node metastasis. Moreover, we found that the expression of PYCR1 is highly up-regulated in response to TP53 mutations with hypomethylation of its promoter, thus implying a novel mechanism of transcriptional activation of PYCR1. Notably, the analysis showed that high expression of PYCR1 is an independent marker predicting poor survival. This makes PYCR1 a reliable biomarker with both diagnostic and prognostic value and demonstrates the significance of a metabolic-genetic axis in cancer development. The study concludes that PYCR1 proline pathway modulation can be used as a novel therapy to treat lung adenocarcinoma.

Keywords: Bioinformatics Analysis; Biomarker; DNA Methylation; Lung Adenocarcinoma; Prognostic Biomarker; Proline Metabolism; PYCR1; TCGA; Therapeutic Target; TP53 Mutation; Transcriptomic Analysis; UALCAN.

1.0. Introduction

Adenocarcinoma of the lung (LUAD) is the most common histological type of non-small cell lung cancer (NSCLC), representing the leading cause of death in patients with cancers all over the world [1]. Despite recent successes in development of targeted therapies and inhibitors of immune checkpoints, survival rates at 5 years remain low, because of late diagnosis and acquired resistance to therapy [2]. However, recent studies have shown that metabolic programming, which involves changes in nutrient utilization by cancer cells to facilitate proliferation, is an essential factor in LUAD tumorigenesis [3-4].

One such important change observed in this metabolic program is proline biosynthesis, which serves to help maintain redox balance in addition to generating building blocks [5]. The rate limiting step in this pathway occurs through an enzyme called Pyrroline-5-Carboxylate reductase 1 (PYCR1), which acts to reduce P5C to proline in mitochondria [6].

PYRCR1 was recently reported as a strong oncogene for breast cancer as well as liver cancer, and in conditions of nutrient deprivation or hypoxia, plays a role in maintaining cell survival [7-8]. For instance, in the case of lung cancer, it has been demonstrated that the PYCR1 gene acts as a proliferation enhancer through activation of the JAK/STAT3 signaling pathway [9]. The gene, in addition, has many lncRNA genes that control its regulation, and one such lncRNA is LINC00511 [10]. Yet, no systematic investigations have been undertaken to establish an association between the expression of this gene in certain clinical subgroups.

In this paper, we took advantage of the TCGA data source by using the UALCAN online software tool to conduct a comprehensive analysis of PYCR1 in LUAD [11-12]. This included evaluating its expression based on gender differences, its relationship with nodal metastasis and TP53 mutations, as well as its regulation through DNA promoter methylation [13-14]. The results obtained from this research can serve as an ideal basis for PYCR1 as a universal biomarker and metabolic vulnerability in LUAD treatment.

1.1. Study Objectives

The purpose of the current research was to assess the clinical and epigenetic importance of PYCR1 in the development of lung adenocarcinoma by means of integrated bioinformatics approaches. More specifically, the following objectives were to be achieved:

a) To compare the differential expression of PYCR1 in lung adenocarcinoma tissue samples vs normal lung tissues based on TCGA data.

b) To conduct a pan-cancer assessment of PYCR1 expression patterns in various types of cancer.

c) To estimate the correlation between PYCR1 expression and clinical and pathological features, such as age, gender, race, smoking status, stage, metastatic involvement, and subtypes of lung adenocarcinoma.

d) To find out whether PYCR1 expression correlates with TP53 mutation status in LUAD patients.

e) To assess the influence of the DNA methylation in the PYCR1 gene promoter on PYCR1 expression in tumor vs normal tissues.

f) To perform a survival analysis to test the prognostic value of PYCR1 in LUAD.

g) To estimate the potential of PYCR1 as a diagnostic, prognostic, and therapeutic biomarker for lung adenocarcinoma.

2.0. Literature Review

Cancer cell metabolism has attracted much interest as part of tumor progression, involving metabolic pathway remodeling for cell growth and survival under stress. In terms of this pathway, the focus is now on the metabolic pathway, proline biosynthesis due to its role in cellular biosynthesis and oxidative stress regulation. One of the enzymes involved in this process is the mitochondrial enzyme called pyrroline-5-carboxylate reductase 1 (PYCR1), which catalyzes the conversion of the metabolite pyrroline-5-carboxylate (P5C) to proline. Accumulating evidences show that PYCR1 promotes tumor progression due to cell proliferation and migration, redox homeostasis, and metabolic adaptation [15-16].

The previous works have shown that PYCR1 is associated with the oncogenicity of tumor cells in various types of cancer such as breast, liver, and colorectal cancers. Besides, PYCR1 was found to be responsible for cell proliferation and survival in lung cancer. Thus, PYCR1 might be considered as a significant factor in LUAD progression and a promising biomarker [17].

The newest articles of 2025 and 2026 added more significance to PYCR1 in LUAD. Liu *et al.* (2025) have demonstrated that the transcription factor FOXA1 promoted PYCR1-mediated autophagy, which suppressed

antitumor immunity in lung adenocarcinoma. It means that PYCR1 is involved in tumor development not only as a metabolic but also as an immunomodulatory factor [18]. The second article published in 2025 by Shin *et al.* has revealed that PYCR1 drove lung cancer progression by interaction with the EGFR and Toll-like receptor (TLR) signaling pathways [19].

The newest studies of 2026 have further increased the metabolic significance of PYCR1 in LUAD. Chen *et al.* (2026) have found that PYCR1 promoted glutamine metabolism and LUAD progression by regulating OPLAH expression, proving that PYCR1 is part of a wider metabolic network [20]. Furthermore, Ma *et al.* (2026) have demonstrated that inhibition of PYCR1-mediated proline metabolism slowed down LUAD progression, which suggests that PYCR1 can be considered a promising drug target 21]. Overall, all these evidences highlight the importance of PYCR1 for LUAD pathogenesis via metabolic remodeling, autophagy, and oncogenic signaling.

Nevertheless, there are several aspects of the role of PYCR1 in LUAD development still unknown. So far, the vast majority of studies have concentrated on experimental models of LUAD, and the clinical relevance and epigenetic regulation of PYCR1 in LUAD has not been investigated in depth. Especially, there is a lack of data concerning the connection of PYCR1 with clinicopathological parameters, TP53 mutation, methylation of PYCR1 promoter and survival of LUAD patients. As TP53 mutations and abnormal DNA methylation are quite frequent events in the development of lung adenocarcinoma, the analysis of the link between them and PYCR1 may reveal significant features of LUAD progression [22].

Thus, in the current study, the bioinformatic analysis of PYCR1 in LUAD will be conducted on the basis of UALCAN database with TCGA data. Through evaluation of differential expression, clinicopathological associations, TP53 mutation relevance, promoter methylation and prognostic value of PYCR1, the diagnostic, prognostic and therapeutic potential of PYCR1 as biomarker in LUAD will be determined.

3.0. Materials and Methods

3.1. Data Acquisition and Bioinformatics Analysis

Genes' expression, clinical pathophysiology, survival rates, mutations, and DNA methylation data used in this paper were collected from Cancer Genome Atlas (TCGA) database of LUAD by use of online analysis website, UALCAN [11]. UALCAN database is an online analytics platform that allows users to access analyzed and normalized RNA sequences in TPMs [12].

3.2. Differential Expression Analysis

The gene expression of PYCR1 mRNAs was analyzed in primary LUAD tumor tissues (n = 515) and normal lung tissue controls (n = 59). The expression pattern of PYCR1 gene in relation to LUAD was studied by performing pan-cancer analysis using the TCGA data for all types of cancers [21].

3.3. Clinicopathological Subgroup Analysis

Relationships of PYCR1 expression and tumor aggressiveness were analyzed by categorizing the LUAD patients into groups based on different criteria. Age, gender, and race (Caucasian, African-American, and Asian) were

considered as demographic characteristics. Smoking and histopathological type served as clinical characteristics. Disease aggressiveness was examined by staging of the pathology and nodal metastasis status following the classification described in the 8th AJCC edition staging manual [13].

3.4. Genomic and Promoter Methylation Analysis

Genomic stability vs. metabolism correlation studies were done by categorizing PYCR1 expression based on TP53 mutation types (Mutant vs. Wild-type) [17]. Also, PYCR1's epigenetic regulation was studied through evaluating DNA methylation in its promoter region by employing TCGA's DNA methylation beta values (range: 0-1). Differential methylation analysis in primary LUADs vs. normal lungs provided possible transcriptional "on switches" [18-19].

3.5. Survival and Statistical Analysis

The Kaplan-Meier survival analysis was carried out to explore the role of PYCR1 as a prognostic marker in LUAD. The overall survival (OS) comparison between the high expression and low expression groups was performed using the log-rank test [20]. All other statistical analyses were done using the UALCAN web tool, which includes comparisons of two groups via the Student's t-test. p-values ≤ 0.05 were regarded as statistically significant.

4.0. Results and Discussion

4.1. Pan-Cancer Expression Profile of PYCR1

To determine the clinical relevance of PYCR1 in various cancers, we studied the expression pattern of PYCR1 in different cancers using the TCGA dataset available on the UALCAN website. As a result, it can be seen that there is up-regulation of PYCR1 in a number of cancers compared to their normal tissue samples. Some examples include BRCA, LIHC, and STAD. However, what we found is that LUAD has a higher level of PYCR1 than any other form of cancer, which is shown in Figure 1.

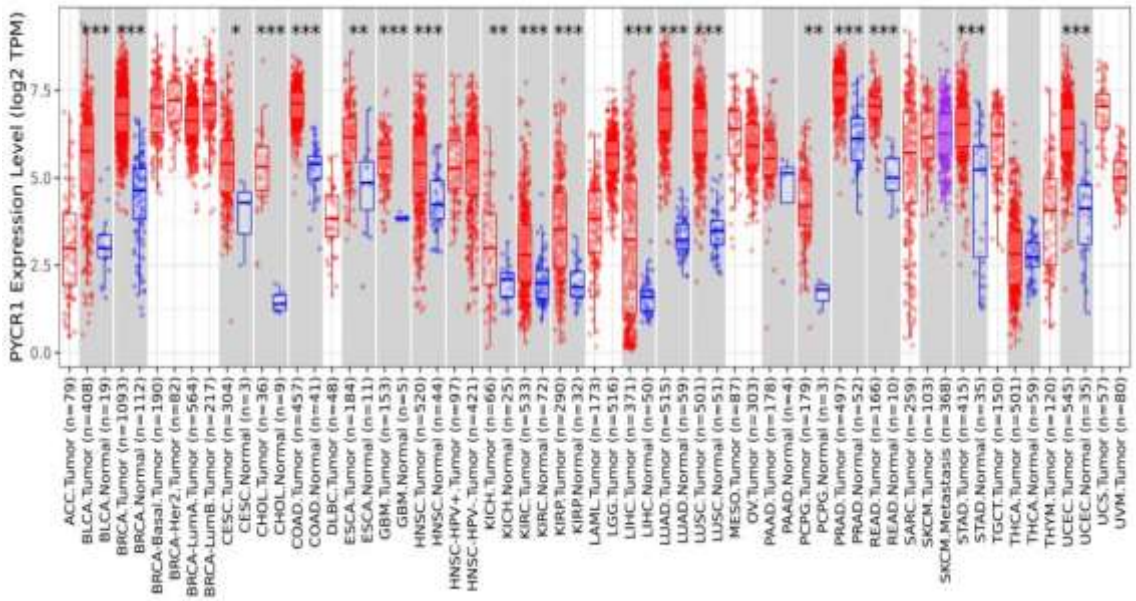

Figure 1. Pan-Cancer Expression Profile of PYCR1 based on TCGA datasets.

The findings revealed that PYCR1 is significantly overexpressed in LUAD tissues compared with normal lung tissues, suggesting that this gene may play an important role in LUAD development. Since PYCR1 is a key enzyme involved in proline biosynthesis, its upregulation may reflect the increased metabolic requirements of rapidly proliferating cancer cells. This observation is consistent with the concept that metabolic reprogramming is one of the major hallmarks of cancer and contributes to tumor growth, redox balance, and adaptation to cellular stress.

4.2. Significant Upregulation of PYCR1 in LUAD

We further explored the levels of PYCR1 expression in the LUAD sample set. Transcriptome profiling of the mRNA transcripts, measured in TPMs, demonstrated a marked discrepancy between the tumor tissue samples (n=515) and the lung normal tissue samples (n=59). PYCR1 was found to be upregulated in the tumor sample group relative to the normal sample group ($p < 0.05$). confirming its status as a highly expressed biomarker in lung adenocarcinoma and represented in Figure 2.

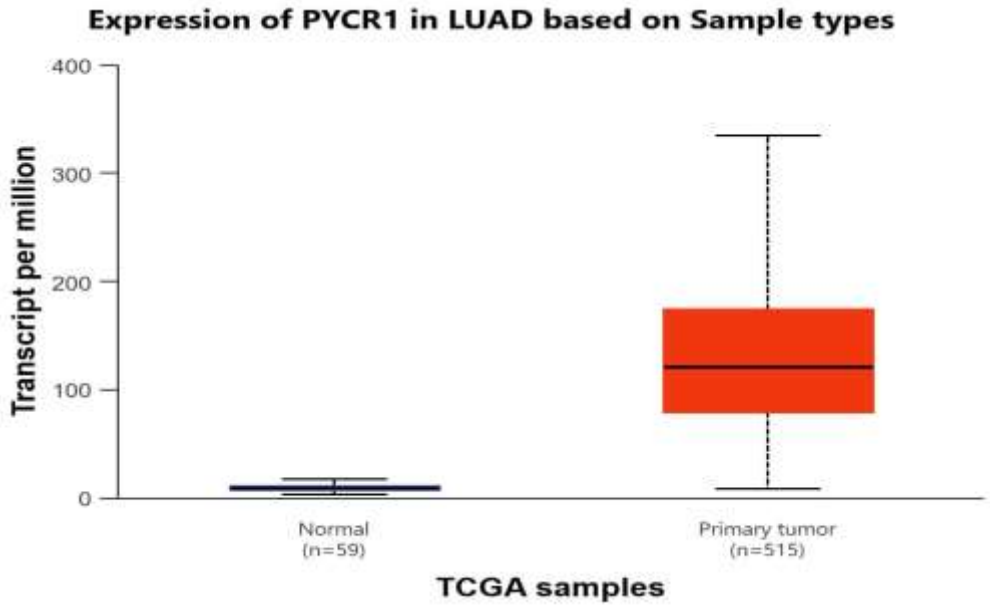

Figure 2. Differential expression of PYCR1 in normal lung and LUAD primary tumor tissues.

The higher PYCR1 expression in LUAD tumor tissues compared to normal lung tissues indicates the involvement of PYCR1 in the development of LUAD. The increase in PYCR1 expression might be related to the increased metabolism requirements in cancer cells, considering the function of PYCR1 in proline metabolism and redox balance in cells. Despite the fact that PYCR1 is correlated with the metabolism changes in tumors, its prognosis significance in LUAD has not been confirmed in the current study.

4.3. Association with Demographic Factors

To determine if PYCR1 expression is influenced by patient characteristics, the data was stratified by gender, age, race, and smoking history. The PYCR1 gene was found to have similar levels of high expression in both genders, which is illustrated in Fig. 3(a). This gene has similar levels of expression among Caucasians, African-Americans, and Asians, which is represented in Fig. 3(b). Elevated levels were recorded for all age groups, shown in Fig. 3(c), but the highest median expression level was recorded among individuals aged between 41 and 60 years (n=90). To

our surprise, although the transcripts were upregulated in current smokers (n=118), the transcripts were also significantly upregulated in former smokers and nonsmokers (n=75). Thus, the activation of PYCR1 is not associated with a history of smoking, which is given in Fig. 3(d).

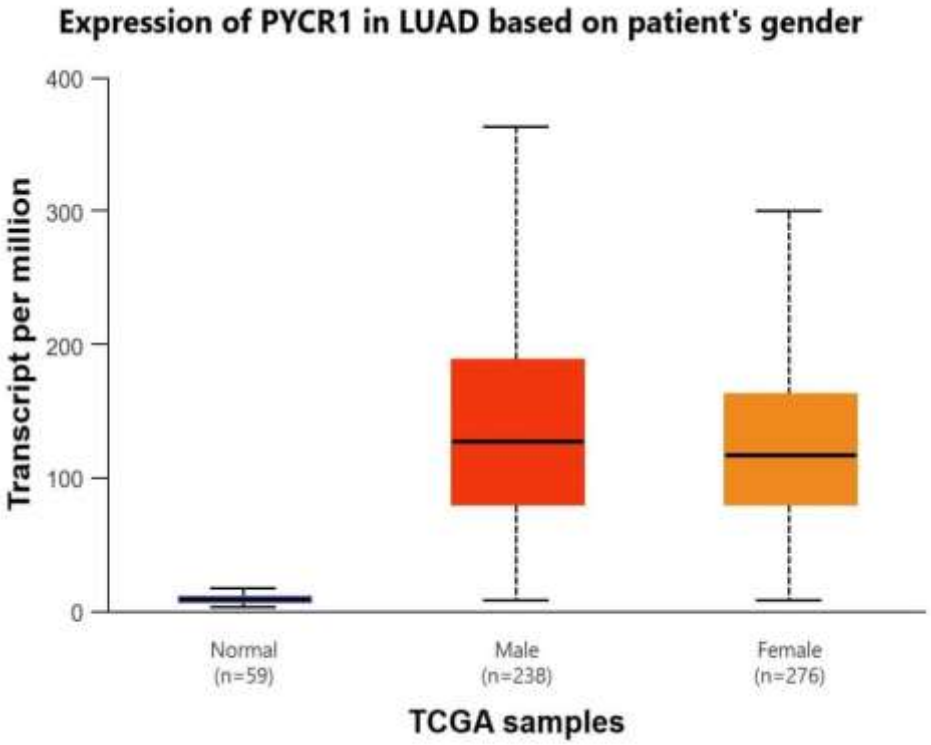

Figure 3(a). Expression pattern of PYCR1 across gender subgroups of LUAD patients.

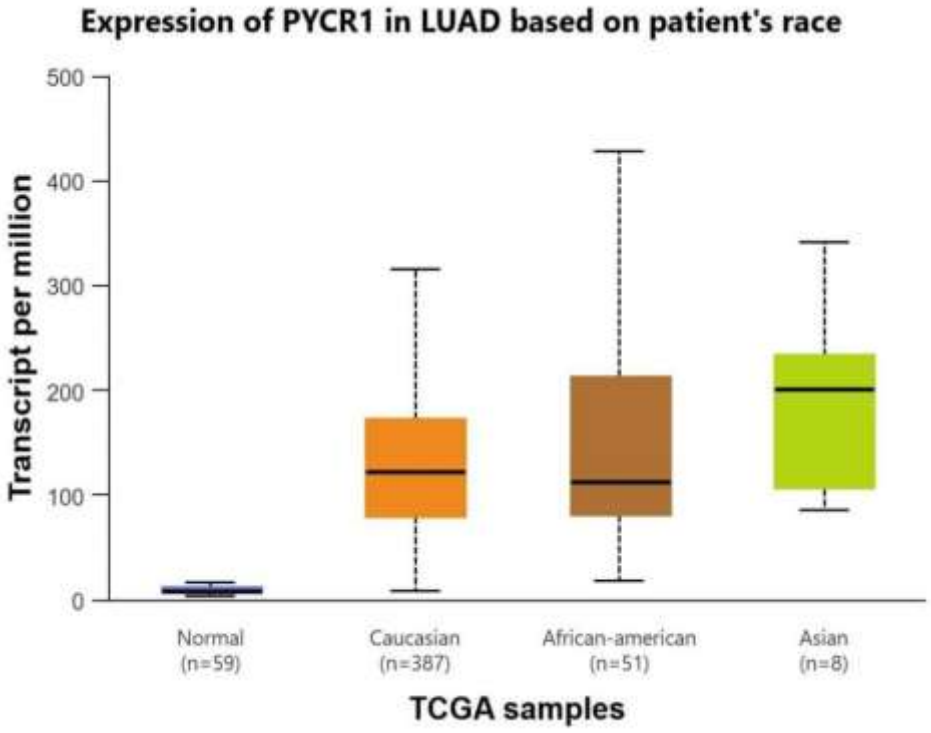

Figure 3(b). Expression pattern of PYCR1 across race subgroups of LUAD patients.

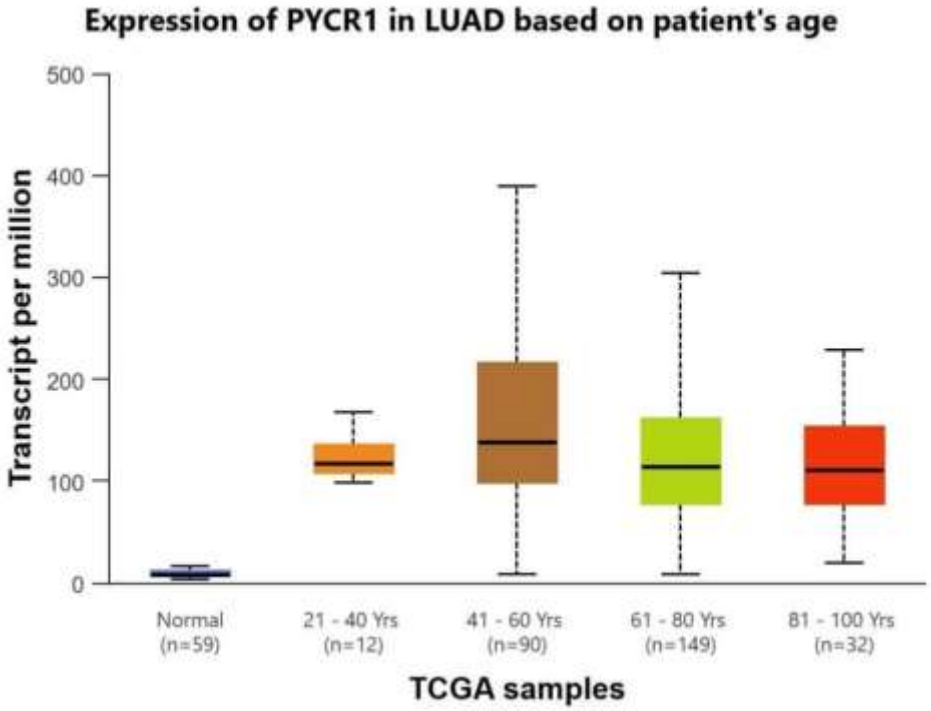

Figure 3(c). Expression pattern of PYCR1 across age subgroups of LUAD patients.

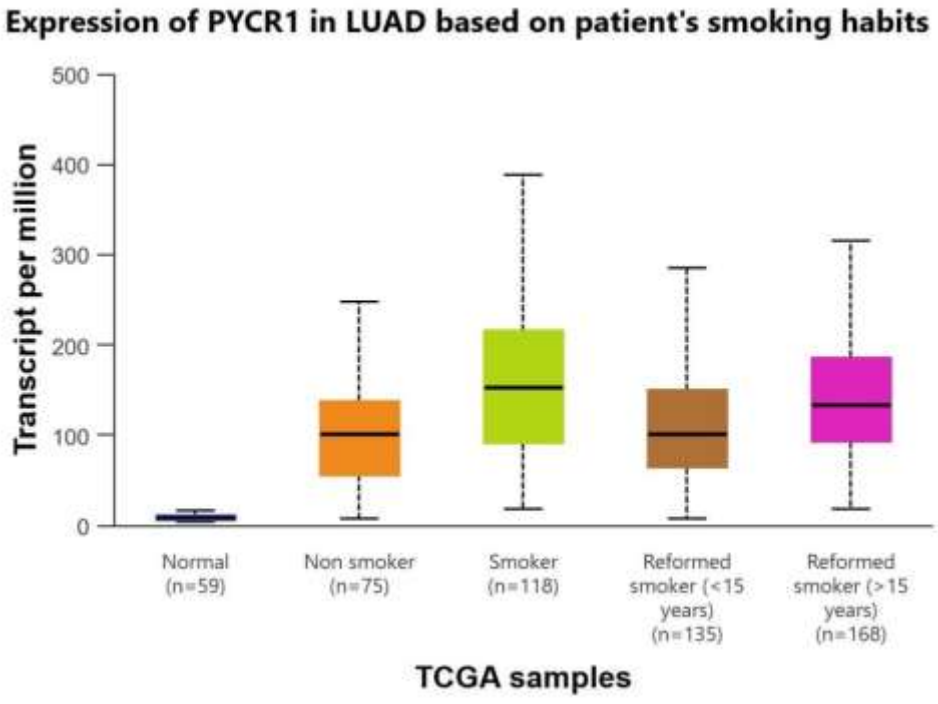

Figure 3(d). Expression pattern of PYCR1 across smoking subgroups of LUAD patients.

Another important finding of the present study is that PYCR1 expression remained elevated across all clinicopathological subgroups, regardless of age, gender, race, and smoking status. This consistent overexpression suggests that PYCR1 may serve as a relatively stable biomarker in LUAD and is not restricted to a particular patient subgroup. The absence of major differences according to smoking history is also notable, indicating that PYCR1 activation may be associated with LUAD progression independently of smoking-related carcinogenesis.

4.4. Correlation with Clinical Stage and Metastasis

The link between the expression level of the PYCR1 gene and the disease severity was determined. In the course of the study on the pathogenesis of the disease stages, the following was shown in Fig. 4(a) and found: a gradual increase in the PYCR1 expression level was registered as it progressed from Stages 1 to 3. Besides, concerning the nodal metastasis staging represented on Fig. 4(b), an increase in the PYCR1 expression level was revealed while it progressed from N0 to N3 stages. It was determined that the maximum PYCR1 expression level was registered in N3 stage patients (n=2).

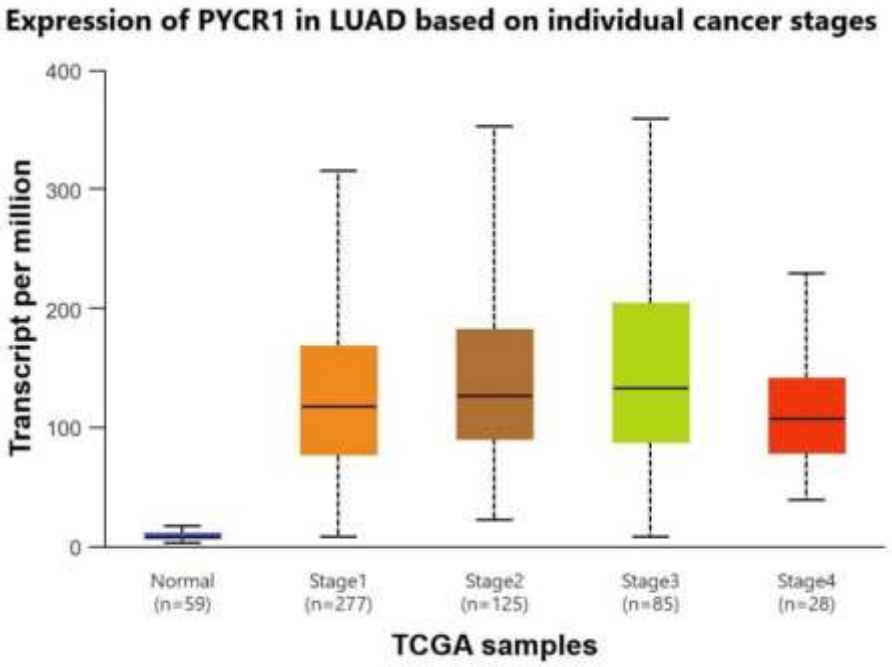

Figure 4(a). Correlation of PYCR1 expression with tumor stage in LUAD.

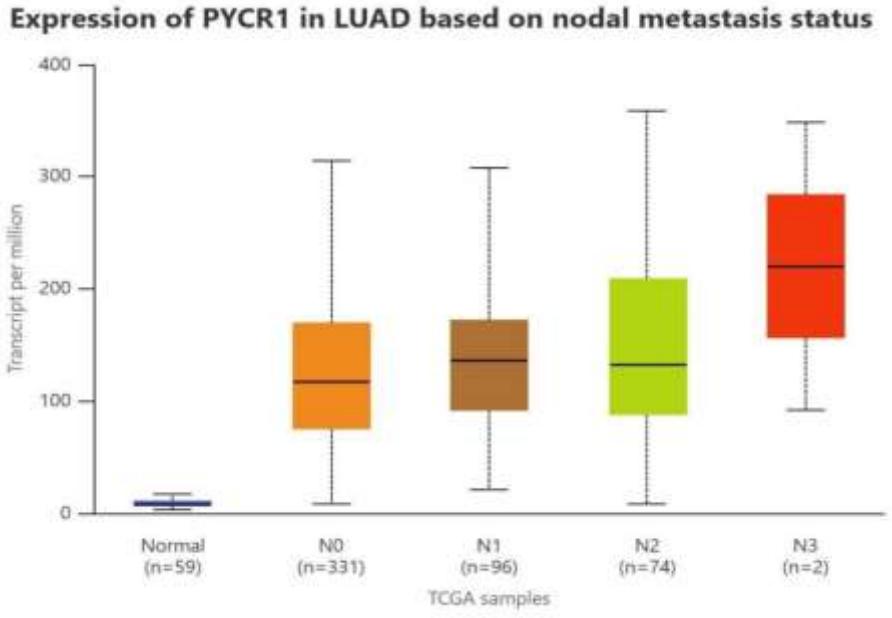

Figure 4(b). Correlation of PYCR1 expression with nodal metastasis in LUAD.

The present analysis further showed that high PYCR1 expression was associated with advanced tumor stage and nodal metastasis, indicating a possible role in disease aggressiveness. Tumor cells undergoing metastatic progression require substantial metabolic adaptation to support migration, invasion, and survival in new microenvironments. Because PYCR1 is involved in proline metabolism and redox homeostasis, its overexpression may help LUAD cells tolerate oxidative stress and fulfill the biosynthetic demands necessary for successful metastatic spread. Therefore, the elevated expression of PYCR1 in advanced-stage and lymph node-positive tumors supports its possible involvement in tumor progression and metastasis.

4.5. Histological Subtype and Genetic Alterations

Expression of PYCR1 showed, in Fig. 5(a), a differential pattern among various histopathological patterns within LUAD. Increased PYCR1 levels were observed in both Clear Cell Pattern (n=2) and Solid Pattern Predominant Pattern (n=5). On genome-wide analysis shown on Fig. 5(b), it was found that PYCR1 was highly expressed in tumors with TP53 mutation (n=233) in comparison to wild-type TP53 (n=279), thereby implying that the inhibition of p53 function could induce metabolism alteration through PYCR1.

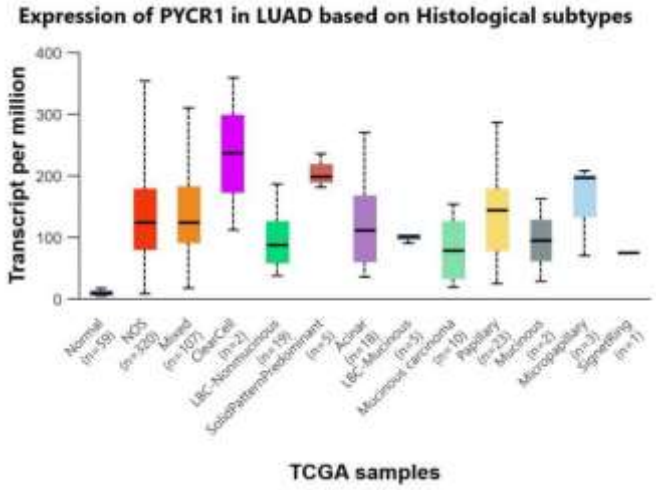

Figure 5(a). Relationship of PYCR1 expression with histological subtypes in LUAD.

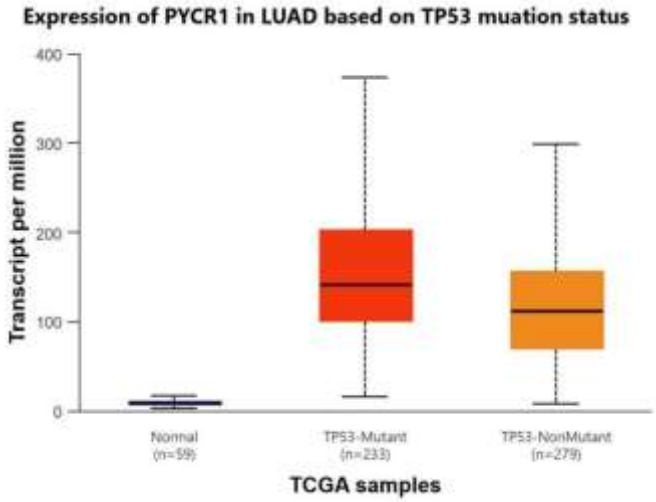

Figure 5(b). Relationship of PYCR1 expression with TP53 mutation status in LUAD.

Another notable finding was the association between PYCR1 overexpression and TP53 mutation status. TP53 is one of the most frequently altered tumor suppressor genes in LUAD and plays a central role in regulating cell cycle progression, apoptosis, and metabolism. The higher expression of PYCR1 observed in TP53-mutant tumors may indicate that p53 dysfunction contributes to metabolic imbalance and promotes PYCR1 activation. This relationship suggests that PYCR1 may be involved in the interaction between metabolic rewiring and genomic instability in LUAD. However, further mechanistic studies are required to clarify the direct regulatory relationship between TP53 and PYCR1.

4.6. Epigenetic Regulation via Promoter Hypomethylation

In order to elucidate the process underlying the induction of PYCR1 mRNA expression, an analysis was conducted on the methylation level of the PYCR1 promoter sequence (Fig. 6). The findings suggested that the promoter region is hypomethylated, evidenced by low beta levels in primary LUAD tumors (n=473) as compared to normal lung tissues (n=32). This epigenetic alteration likely facilitates transcriptional activation and the subsequent overexpression of PYCR1 in cancerous cells.

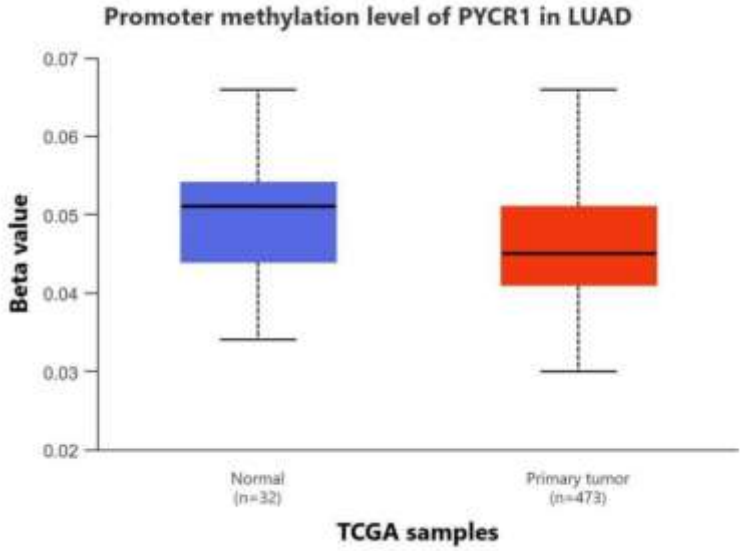

Figure 6. Relationship of PYCR1 expression with promoter methylation status in LUAD.

In addition, the present study identified promoter hypomethylation of PYCR1 in LUAD tissues, suggesting a possible epigenetic mechanism underlying its increased expression. DNA methylation is an important regulator of gene transcription, and promoter hypomethylation is often associated with activation of oncogenes in cancer. Therefore, the reduced methylation level observed in the PYCR1 promoter region may have contributed to its transcriptional upregulation in LUAD. This finding is important because it indicates that PYCR1 overexpression may result not only from metabolic demand or signaling alterations, but also from epigenetic deregulation. Such epigenetic activation further strengthens the relevance of PYCR1 as a potential biomarker and therapeutic target.

4.7. Survival Analysis of PYCR1 Expression in LUAD

Kaplan-Meier survival analysis was carried out in order to evaluate the significance of PYCR1 expression in lung adenocarcinoma (LUAD). The patient population was divided into the high (n=126) and low/moderate (n=376)

PYCR1 expression groups according to their respective levels of PYCR1 expression. The overall survival between the two groups was compared, and it was found that the survival curves between the two groups overlapped extensively throughout the observation period without any significant difference (p=0.87). More specifically, the probability of 5-year survival rate in the high PYCR1 expression group was 39% and that in the low/moderate PYCR1 expression group was 41%, which is shown in Fig. 7.

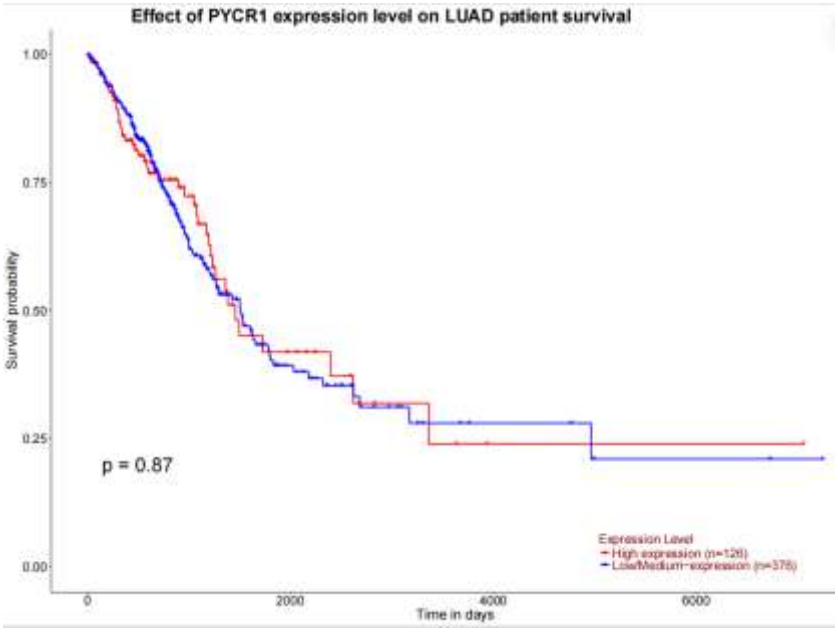

Figure 7. Prognostic significance of PYCR1 expression in LUAD: Kaplan–Meier overall survival analysis.

Survival analysis in the present study revealed that high PYCR1 expression was associated with poorer overall survival in LUAD patients, further supporting its prognostic significance. Biomarkers that are associated with both tumor aggressiveness and patient outcome are particularly valuable because they may help identify high-risk patient groups and guide clinical decision-making. The poor survival associated with elevated PYCR1 suggests that its biological role may extend beyond metabolic adaptation and may actively contribute to aggressive tumor behavior.

Taken together, the findings of this study indicate that PYCR1 is involved in multiple aspects of LUAD biology, including tumor metabolism, disease progression, epigenetic regulation, and prognosis. The association of PYCR1 overexpression with clinicopathological features, TP53 mutation, promoter hypomethylation, and poor survival makes it a promising candidate for biomarker development in LUAD. In addition, because PYCR1 is a metabolic enzyme, it may also serve as a potential therapeutic target.

5.0. Conclusion and Further Studies

An integrated bioinformatics analysis was carried out in the current study to explore the clinical and epigenetic role of PYCR1 in lung adenocarcinoma (LUAD). It is shown that PYCR1 was significantly upregulated in LUAD tissue samples in comparison with the normal lung tissues, and remained overexpressed among various clinicopathological categories. The higher PYCR1 expression level was linked to the higher stage of tumor development, nodal metastasis, TP53 mutant status, promoter hypomethylation, and poor overall survival rate, demonstrating its potential role in the progress of LUAD.

All of this suggests that PYCR1 could be considered as a prospective diagnostic and prognostic marker in lung adenocarcinoma. As one of the major enzymes of proline metabolism, PYCR1 could play a role in metabolic reprogramming, development, and metastasis of LUAD cells. Moreover, PYCR1 involvement in the TP53 mutation and promoter hypomethylation indicates the possibility of genetic and epigenetic regulation of PYCR1 in LUAD.

Though there are some important results in the current study, there are several limitations which should be noted. Mainly, this study used the publicly available transcriptomic and clinical data as the basis for bioinformatics analysis. Thus, the results of this study need to be verified in future. Experimental studies aimed at the verification of PYCR1 overexpression in LUAD tissues and cell lines using the techniques like qRT-PCR, Western blotting, and immunohistochemistry are needed. There should also be functional studies on PYCR1 which would explain the role of PYCR1 in LUAD cell proliferation, invasion, metastasis, and metabolic adaptation. In addition, the studies on the connection between PYCR1, TP53 mutation status, promoter methylation, autophagy, and tumor immunity will help us to understand better the molecular mechanism of PYCR1 involvement in LUAD.

Conclusively, this review provides the evidence of PYCR1 being an important marker as well as a potential target in the diagnosis and treatment of lung adenocarcinoma. Improved knowledge about the mechanism of PYCR1-mediated metabolism and epigenetics could contribute to the development of more precise diagnostic tests and therapeutic methods for LUAD patients.

Some areas that require future research include:

a) Validation of PYCR1 expression in LUAD tissues and cell lines by means of qRT-PCR, Western blotting and immunohistochemistry techniques.

b) Investigations into PYCR1 function to find out its roles in LUAD cell proliferation, migration, invasion, apoptosis and metastasis.

c) Investigations into PYCR1-related metabolic pathways with a special emphasis on its participation in proline metabolism, redox homeostasis and glutamine metabolism in LUAD.

d) Validation of the correlation between PYCR1 expression and TP53 mutation status in order to elucidate the connection between PYCR1-mediated metabolic regulation and genomic instability in LUAD.

e) Epigenetic studies of PYCR1 promoter methylation in order to find out whether hypomethylation is responsible for PYCR1 overexpression in LUAD.

f) Investigations into PYCR1 in the context of autophagy and immune regulation with a special emphasis on its interaction with LUAD cell immune escape mechanisms.

g) PYCR1 as a therapeutic target: Testing of inhibitors or metabolic pathway targeting agents on preclinical LUAD models.

h) Large clinical validation studies of PYCR1 as a diagnostic and prognostic marker of LUAD.

Declarations

Source of Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing Interests Statement

The authors declare that they have no competing interests related to this work.

Consent for Publication

The authors declare that they consented to the publication of this study.

Authors' Contributions

Md. Mahbubol Alam and Rifah Tamanna Begum took part in literature review, conceptualization, methodology, investigation, analysis, and manuscript writing and editing. Sumon Ahmed Suvo, Fahamida Binta Anower and Sahariare Nazim analyzed data. Md. Fardin Islam and Md. Imam Mahdi Ratul were involved in the design of the manuscript. Md. Mahbubol Alam and Fahamida Binta Anower reviewed the manuscript. All authors have read and approved the final manuscript.

Availability of Data and Materials

Supplementary information is available from the authors upon reasonable request.

Institutional Review Board Statement

Not applicable.

Ethical Approval

Not applicable for this study.

Informed Consent

Not applicable for this study.

Declaration of Artificial Intelligence

No AI tools were used for this study.

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